Antibiotic Use During Pregnancy and Lactation

*Sorting Fact from Fiction*

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### Obstetric Challenges
- Infections: common in obstetrics
- Antibiotics: prescribed in pregnancy/lactation
- Limited studies in pregnant women
- Most safety data is observational
- Limited randomized trials
- Limited use of newer antibiotics
- Perception that few antibiotics safe in pregnancy

Andrade 2004

### Overview
- Pharmacokinetics of Pregnancy
- Drug Safety Classification System
- Safety and use in Pregnancy
- Safety and use in Breastfeeding
- Specific infections/treatments
  - Cystitis, pyelonephritis
  - Pneumonia, tuberculosis
  - BV, syphilis, GC, CT
  - Mastitis

### Overview of Antibiotics
- Penicillins
- Cephalosporins
- Macrolides
- Aminoglycosides
- Quinolones
- Other antibiotics
  - Chloramphenicol
  - Clindamycin
  - Nitrofurantoin
  - Rifampin
  - Vancomycin
Pharmacokinetics of Pregnancy

- Physiologic changes on antibiotic PK
  - Serum and tissue levels
  - Excretion
  - Accumulation
- Fall in plasma protein 1 g/100 ml
  - Decreased drug binding
- Intravascular volume increase
  - Increased cardiac output and GFR
  - ↑ drug clearance/lower serum levels
- Antibiotics: lipid soluble and low molecular wt
  - Facilitate placental crossing

Physiologic changes on antibiotic PK

- Lower Serum Levels
  - Penicillins
  - Ampicillin
  - Amoxicillin
  - Cephalosporins
  - Erythromycin
  - Gentamicin
  - Other aminoglycosides
  - Nitrofurantoin
  - Quinolones

Uncertain safety

- Other aminoglycosides

A: No adverse effects in human pregnancies
- Safety established using well-controlled human studies

B: Presumed safety in human pregnancies
- Limited human studies/no adverse effects in animal studies

C: Uncertain safety
- Limited human studies/adverse effects in animal studies

D: Adverse effects in pregnancies
- Benefits may outweigh associated risks

X: Adverse effects in pregnancies
- Risks outweigh possible benefit

FDA Classification: Drug Safety in Pregnancy

21 CFR 201.57
Classifications: Drug Safety in Lactation

+: Generally accepted as safe
?: Safety unknown or controversial
-: Generally regarded as unsafe

Penicillins and Pregnancy

Examples: PCN G, PCN V, amoxicillin, ampicillin

General pharmacokinetics in pregnancy
- Lower serum levels
  Vol of dist/renal clearance increased in 2nd & 3rd trimesters

Placental transfer: crosses

Teratogenicity: none-unlikely
- No increased risk of congenital anomalies
- ?Association with NEC in preterm infants born to mothers on amoxicillin-clavulanic acid in 3rd trimester

Cephalosporins and Pregnancy

Examples: cephalaxin, cefazolin

General pharmacokinetics in pregnancy
- Lower serum levels

Placental transfer: crosses

Teratogenicity: unlikely
- Most studies demonstrate no increase in congenital defects or toxicity to newborn
- Few studies: ?small increase in congenital anomalies
  Poorly designed; no evaluation of confounders; recall bias

Macrolides and Pregnancy

Examples: erythromycin, azithromycin

General pharmacokinetics in pregnancy
- Lower serum levels

Placental transfer: crosses

Teratogenicity: none-unlikely
- No association with congenital anomalies
- Estolate salt formulation
  Associated with hepatotoxicity in pregnant women

Paterson 1972; Creatsas 1980; Pfau 1992; Rosa 1993


Jacobson 2001; Kaemmer 2001; Rahangdale 2006; CDC 2006; Briggs 1998; McCormack 1977; Collaborative Perinatal Project
### Aminoglycosides and Pregnancy
- Examples: gentamicin, streptomycin
- General pharmacokinetics in pregnancy
  - Lower serum levels and decreased half-life
  - Clearance decreased in preeclamptic patients
  - Check peak/trough levels
- Placental transfer: crosses
- Teratogenicity: undetermined/limited data
  - Streptomycin: Case series of variable human ototoxic effects
  - Gentamicin: No increase in congenital anomalies, ototoxicity, nephrotoxicity in human studies
  - Toxicity demonstrated in animal studies

### Tetracyclines and Pregnancy
- Examples: tetracycline, doxycycline, minocycline
- General pharmacokinetics in pregnancy
  - Unknown
- Placental transfer: crosses
- Teratogenicity: unlikely
  - May induce hepatic necrosis in pregnant women
  - May cause teeth staining, enamel hypoplasia, and reversible depression of fetal bone growth
  - Skeletal anomalies in animals (17x MRHD)
  - Doxycycline: No association with congenital anomalies
  - Doxycycline: No reports of teeth staining in humans!

### Quinolones and Pregnancy
- Examples: ciprofloxacin, levofloxacin, ofloxacin
- General pharmacokinetics in pregnancy
  - Lower serum levels
- Placental transfer: crosses
- Teratogenicity: unlikely
  - No significant increase or trends in congenital anomalies in human studies (cipro, oflox)
  - Cipro: No adverse effects in animal studies
  - Levo: Fetal skeletal ossification retardation, skeletal variations, decreased weight, increased mortality in rats
    - 810 mg/kg/day dose (>9x MRHD)
- Levofloxacin human studies limited

### Other Antibiotics and Pregnancy
- Chloramphenicol
- Clindamycin
- Nitrofurantoin
- Rifampin
- Vancomycin
**Chloramphenicol and Pregnancy**

- General pharmacokinetics in pregnancy
  - Unknown
- Placental transfer: crosses
- Teratogenicity: unlikely
  - No significant risk of congenital anomalies
  - Potential bone marrow suppression in infant
  - Avoid near term, during labor, and in breastfeeding

Numah 2006; Weiss 1960; Czeizel 2000; Heinonen 1977; Courtney 1968; Fritz 1971; Prochazka 1964

**Clindamycin and Pregnancy**

- General pharmacokinetics in pregnancy
  - No change
- Placental transfer: crosses
- Teratogenicity: undetermined/unlikely
  - No increased risk of congenital anomalies
  - Causative factor for development of C. diff
  - No difference in pregnant versus non-pregnant women

Numah 2006; Rosa 1993; McGready 2001; McCormack 1987; Ou 2001; Rothman 1988

**Nitrofurantoin and Pregnancy**

- General pharmacokinetics in pregnancy
  - Lower serum levels
- Placental transfer: crosses
- Teratogenicity: unlikely
  - Rare adverse effect: pulmonary hypersensitivity
  - No increased risk of congenital anomalies
  - May induce hemolytic anemia in G6PD deficiency
  - No case of hemolytic anemia of newborn due to in-utero exposure!

Landers 1983; Philipson 1982; Briggs 1998; Prytherch 1969; Rosa 1993

**Rifampin and Pregnancy**

- General pharmacokinetics in pregnancy
  - Unknown
- Placental transfer: crosses
- Teratogenicity: unlikely
  - No increased risk of congenital anomalies

Numah 2006; Stevenson 1959; Steen 1977; Bhargava 1996; Khan 2001
Vancomycin and Pregnancy

- General pharmacokinetics in pregnancy
  - Unchanged
- Placental transfer: crosses
- Teratogenicity: undetermined/unlikely
  - No significant risk of congenital anomalies
  - No change in risk of ototoxicity or nephrotoxicity in pregnant versus non-pregnant women
  - Risk of toxicities to fetus considered low

Breastfeeding and Antibiotics: Pharmacodynamics

- Factors affecting medication transfer into milk
  - Medication dose timing
  - Bioavailability
  - Maternal Clearance
- Drugs most likely to be transferred
  - Non-ionized
  - Non-protein bound
  - Low molecular weight
  - High lipid solubility
  - High pH
- Antibiotics DO NOT affect breast milk supply

Breastfeeding and Antibiotics

- Most antibiotics compatible with breastfeeding
- Many used therapeutically in infants
- Potential adverse effects in infants
  - Changes in intestinal flora
- Common antimicrobials safe in breastfeeding
  - Penicillins
  - Cephalosporins
  - Macrolides
  - Aminoglycosides
- Use controversial???
  - Ofloxacin/Quinolones
  - Metronidazole

Breastfeeding and Antibiotics: Ofloxacin

- Found in breast milk
- Associated with arthropathy in juvenile animals
- Risk of arthropathy in infants extremely low
  - Case series >7000 children on chronic quinolones
    - ONLY 10/7000 developed arthropathy-like syndrome
- Bottom line: **Compatible with breast-feeding**

Ingham 1977; Burkhardt 1997; AAP Committee on Drugs 2001
Breastfeeding and Antibiotics: Metronidazole/Tinidazole

- Association with carcinogenesis in rodents
- No cancer association in humans
- No significant increase in adverse events
  - Trend toward loose stools and candidal colonization in metronidazole-exposed infants
- Bottom line: Compatible with breastfeeding
  - Express/discard milk x 24 hours when 2 gm dosing

Passmore 1988; Einarson 2000

Breastfeeding and Antibiotics: Medications to Avoid

- Chloramphenicol
  - Breastfeeding safety unknown
  - Concern for potential bone marrow suppression
  - “Gray-baby” syndrome
  - Use not recommended in breastfeeding by AAP
- Tetracycline
  - Chronic use NOT recommended
  - May cause staining of immature teeth in infants
  - Short-term use compatible with breastfeeding!

AAP Committee on Drugs 1994, 2001; Weiss 1960

Breastfeeding and Antibiotics: Compatible Medications

| Acyclovir | Ciprofloxacin | Ofloxacin |
| Amoxicillin | Clindamycin | Quinidine |
| Aztreonam | Dapsone | Quinine |
| Cefazolin | Erythromycin | Rifampin |
| Cefotaxime | Ethambutol | Streptomycin |
| Cefotixin | Fluconazole | Sulbactam |
| Cefprozil | Gentamicin | Sulfadiazine |
| Ceftazidime | Isoniazid | Sulfoisoxazole |
| Ceftriaxone | Kanamycin | Tetracycline |
| Chloroquine | Nitrofurantoin | TMX-SMX |

AAP Committee on Drugs, Pediatrics 2001

Cystitis Treatment

- Nitrofurantoin
  - Rare adverse effect: pulmonary hypersensitivity
- Cephalosporins
- Penicillins
- Trimethoprim-sulfamethoxazole (TMX-SMX)
  - Sulfonamides
    - Theoretical risk: displaces bilirubin → kernicterus
    - No cases of human kernicterus!
    - No association with birth defects
  - Trimethoprim: Folic acid antagonist
    - Ensure folic acid supplementation if used in first trimester
- Quinolones?
- Duration: 3-7 days

Bogess 1996; Patterson 1997
**Pyelonephritis Treatment**

- Penicillins
- Cephalosporins
- Gentamicin
- Quinolones?
- Duration
  - IV x 48 hours afebrile
  - Change to PO
  - 10-14 days total treatment

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**Pneumonia Treatment**

- Azithromycin
- Amoxicillin
- Amoxicillin-clavulanic acid
- Ceftriaxone
- Doxycycline?
- Quinolones?

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**Tuberculosis: Preventive Therapy**

- Isoniazid (INH)
  - Crosses placenta
  - No increased toxicity to fetus
  - Breastfeeding compatible
  - Possible increase in hepatic toxicity in women
- Bottom line: Postponed until after delivery
  - Exceptions
    - HIV infection
    - Recent PPD conversion with known TB contact

Snider 1992; Brost 1997

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**Bacterial Vaginosis Treatment**

- Recommended regimens
  - Metronidazole (500 mg po BID x 7 days)
  - Metronidazole (250 mg po TID x 7 days)
  - Clindamycin (300 mg po BID x 7 days)
- Metronidazole
  - No teratogenic association demonstrated!
  - Single 2 gram dose not effective for BV tx
- Oral therapy preferred over vaginal
- Clindamycin cream use in 2nd and 3rd trimesters
  - Associated with increased adverse events
  - LBW, neonatal infections

CDC 2006; Caro-Paton 1997; Burtin 1995; Piper 1993; Lamont 2003; McGregor 1994; Joesoef 1995; Vermeulen 1999
Bacterial STD Treatment: Syphilis

- Benzathine Penicillin G
- **No proven alternatives during pregnancy!**
- History of PCN allergy
  - Skin testing
  - PCN desensitization

CDC 2006

Bacterial STD Treatment: Chlamydia

- **First Line**
  - Azithromycin (1 gram po single dose)
  - Amoxicillin (500 mg po TID x 7 days)
- **Second Line**
  - Erythromycin base/ethylsuccinate
  - GI symptoms → non-compliance
- **Less favored or avoided**
  - Doxycycline
  - Quinolones
  - Erythromycin estolate
    - Associated with hepatotoxicity in pregnancy

Jacobson 2001; Kacmar 2001; Rahangdale 2006; CDC 2006

Bacterial STD Treatment: Gonorrhea

- 3rd generation Cephalosporin
  - Ceftriaxone 125 mg IM
  - Cefixime 400 mg PO
- High-risk PCN allergy
  - Spectinomycin 2g IM (CDC)
  - Azithromycin 2 g PO
- If unknown Chlamydia status
  - Treat presumptively for co-infection
- **Quinolones**
  - No longer recommended in US due to resistance!

CDC 2006; CDC 2007

Mastitis Treatment

- **First line**
  - Dicloxacillin
- No response in 24-48 hours
  - Cephalexin
  - Augmentin
- **Mild PCN allergy**
  - Cephalexin
- **High-risk PCN allergy or MRSA infections**
  - TMX-SMX
  - Clindamycin
**Summary**

- Significant PK changes in pregnancy
- Dose antibiotics on upper limits if possible
- Virtually all antibiotics cross placenta
- Virtually all antibiotics found in breast milk
- Many abx are overall safe for use in pregnancy
- Quinolones and doxycycline
  - May be considered for treatment in pregnancy if other alternatives not available

**UCSF Reproductive Infectious Disease Consult Service**

- **1-415-719-8726**
  - Free
  - 24-hour availability
  - For medical providers seeking assistance in management of reproductive infectious disease and perinatal HIV issues

**Summary**

- Most abx may be used in breastfeeding
- Avoid chronic tetracyclines use in breastfeeding
- Avoid use of chloramphenicol in breastfeeding
- Quinolones compatible with breastfeeding
- Metronidazole compatible with breastfeeding
- Review actual risks versus benefits w/ patient
- Utilize risk vs. benefit for management decision

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